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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/607,583	06/25/2003	Kai Y. Xu	A9422	5808

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EXAMINER	
SKELDING, ZACHARY S	
ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/607,583	XU, KAI Y.	
	Examiner	Art Unit	
	ZACHARY SKELDING	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3-31-08 2-29-08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4 and 7-47* is/are pending in the application.

4a) Of the above claim(s) *8-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4 and 7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 29, 2008 has been entered.

2. Applicant's amendment to the claims and remarks filed February 29, 2008 are

   acknowledged.

   Claims 1 and 4 have been amended.

   Claims 2, 5 and 6 have been canceled.

   Claims 1, 3, 4, and 7-47 are pending.

   Claims 8-47 are withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b), as being directed to a non-elected invention.

   Claims 1, 3, 4 and 7 are under examination as they read on an antibody which specifically binds to the amino acid sequence comprising RSATEEEPPNDD of the α-subunit of $(Na^{+}+K^{+})$-ATPase wherein binding of the antibody to the amino acid sequence RSATEEEPPNDD of the α-subunit of $(Na^{+}+K^{+})$-ATPase increases myocyte intracellular diastolic and systolic calcium.

3. The previous rejections of record can be found in the Office Action mailed October 31, 2007.

   This Office Action is in response to applicant's Request for Continued Examination of applicant's amendment to the claims and remarks filed February 29, 2008.

   The previous rejection under 35 U.S.C. § 102(e) as anticipated by Rosen et al. has been withdrawn in view of applicant's amendment to the claims.

   The previous rejection under 35 U.S.C. § 102(b) as anticipated by Ball et al. has been withdrawn in view of applicant's amendment to the claims.

   The previous rejection under 35 U.S.C. § 102(b) as anticipated by Arystarkhova et al. has been withdrawn in view of applicant's amendment to the claims.

The previous rejection under 35 U.S.C. § 103(a) as unpatentable over Arystarkhova et al. in view of Rosen et al., Schwinger et al., Mohraz et al., Bost et al., Bendayan et al. and the instant specification at page 3, 3rd paragraph and page 43-44, has been withdrawn in view of applicant's amendment to the claims.

4. Claims 1 and 3 are objected to for recite polypeptide sequences that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). Under 37 C.F.R. § 1.821(d), these sequences must be annotated with their sequence identifier, i.e., "SEQ ID NO: 1". See also MPEP § 2422.01 and 2422.03.

Appropriate correction is required.

A New Grounds of Rejection necessitated by applicant's amendment to the claims is put forth below. In particular, Arystarkhova now anticipates all the claims under examination.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1, 3, 4, and 7 are rejected under 35 U.S.C. 102(b) as anticipated by Arystarkhova et al., (J Biol Chem. 1992 Jul 5;267(19):13694-701) as evidenced by Bost et al. (Immunol. Invest. 1988; 17:577-586), Bendayan et al. (J. Histochem. Cytochem. 1995; 43:881-886) and the instant specification at page 3, 3rd paragraph and page 43-44, essentially for the reasons of record as put forth in the Office Action mailed October 31, 2007.

Applicant argues (emphasis in the original): "The Examiner asserts that the "crucial" binding for VG4 are the residues EEEP. This does not mean, however, that these same residues would be crucial for the instant antibodies as these antibodies not only are specific for the peptide of the instant invention, but these antibodies are inotropic antibodies. Thus, even if, assuming *arguendo,* VG4 did bind the instant sequence, neither Arystarkhova nor the combination of references teach or disclose that their antibodies are inotropic antibodies and as such do not meet each claim limitation. As to the Examiner's assertions that there is a slight reduction in affinity regarding substitution of serine for Ala^{112} or proline for Gin^{119}, Applicant respectfully disagrees. The extracts against which VG4 was directed to in the assays described by Arystarkhova are crude microsomes subjected to enzymatic digestion and as such any number of sites could be exposed. The Examiner is basing the rejection on probabilities and possibilities that VG4 may bind the instant sequence, however, as discussed above, VG4 does not cause myocyte contraction and does not disclose each and every claim limitation." (See applicant's remarks filed February 29, 2008).

Applicant's arguments have been considered, but have not been found convincing, essentially for the reasons of record as put forth in the Office Action mailed October 31, 2007.

First, Arystarkhova does not have to "teach or disclose that their antibodies are inotropic antibodies" in order to meet the limitation of the claims in so far as this biological property is inherent to the structure of the monoclonal Vg4 antibody of Arystarkhova.

As essentially stated in the previous Office Action mailed May 17, 2007, given that antibodies can be both specific and cross-reactive with antigens from different species (or even distinct proteins not related to the original antigen) as evidenced by Bost and Bendayan, and further given the extensive homology between rat and human polypeptides (96% identity across 1023 amino acids as shown in the alignment between rat_NaK and human_NaK attached to the Office Action mailed May 17, 2006), indicating an overall conservation of structure, and further given that the residues to which the reference antibody binds, in particular residues EEEP which are critical for Vg4 binding, are conserved between rat and human, the reference antibody would bind to the claimed sequence.

Moreover, given that antibodies which bind to SEQ ID NO: 1 inherently have the particular biological properties recited in the claim 1 when binding to the α subunit of rat Na^++K^+-ATPase as evidenced by the instant specification at page 3, 3rd paragraph and pages 43-44, the antibodies of Arystarkhova would inherently possess inotropic activity upon binding to rat Na^++K^+-ATPase.

Furthermore, with respect to applicant's argument that (emphasis in the original) "as to the Examiner's assertions that there is a slight reduction in affinity regarding substitution of serine for Ala^{112} or proline for Gin^{119}, Applicant respectfully disagrees. The extracts against which VG4 was directed to in the assays described by Arystarkhova are crude microsomes subjected to enzymatic digestion and as such any number of sites could be exposed…" it is respectfully submitted that applicant's argument is so unclear as to be incomprehensible.

As stated in the previous Office Action mailed October 31, 2007, it is a statement of fact that in discussing the results of their efforts to "map the antigenic determinant within the *α* subunit of porcine NaK ATPase" (see page 13698, left column 1st paragraph and Figure 7) which is "evidently composed primarily of contiguous amino acids" using fine-specificity analysis Arystarkhova states, "[o]n either side of this cluster [referring to residues 114-EEEP-117], substitution in rat α1 of serine for Ala^{112} or proline for Gln^{119} reduces affinity slightly relative to that for pig αl." (see column bridging paragraph on page 13700).

Thus, it is unclear how applicant can disagree with this aspect of the previous rejection.

With respect to applicant's contention that (emphasis in the original) "[t]he extracts against which VG4 was directed to in the assays described by Arystarkhova are crude microsomes subjected to enzymatic digestion and as such any number of sites could be exposed. The Examiner is basing the rejection on probabilities and possibilities that VG4 may bind the

instant sequence, however, as discussed above, VG4 does not cause myocyte contraction and does not disclose each and every claim limitation," it is unclear what applicant is arguing.

More particularly, while applicant points to no particular section of Arystarkhova in support of their argument, it does not appear to the examiner that the crude microsomes used to obtain the data displayed in Arystarkhova Figure 7 were subjected to enzymatic digestion.

Moreover, applicant's emphasis on the word "crude" in an apparent attempt to question the validity of the teachings of Arystarkhova is also not convincing in that applicant has not provided any scientific reasoning or objective evidence to challenge the use of crude microsomes as a scientifically valid means to prepare and characterize membrane bound Na^++K^+-ATPase.

In this regard Applicants are reminded that arguments of counsel cannot take the place of factually supported objective evidence. See, e.g., In re Huang, 100 F.3d 135, 139-40, 40 USPQ2d 1685, 1689 (Fed. Cir. 1996); In re De Blauwe, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984).

Lastly, it is noted that amended claim 1 recites (emphasis added), "an isolated antibody which ***specifically binds*** to the amino acid sequence comprising RSATEEEPPNDD of the α-subunit of (Na^++K^+)-ATPase…"

The phrase "specifically binds" is described in the instant specification as follows:

> "…specifically (or selectively) binds" to an antibody or "specifically (or selectively) immunoreactive with," when referring to a protein or peptide, ***refers to a binding reaction that is determinative of the presence of the protein in a heterogeneous population of proteins and other biologics***. Thus, under designated immunoassay conditions, the specified antibodies bind to a particular protein at least two times the background and do not substantially bind in a significant amount to other proteins present in the sample. Specific binding to an antibody under such conditions ***may require*** an antibody that is selected for its specificity for a particular protein. ***For example***, polyclonal antibodies raised to marker "X" from specific species such as rat, mouse, or human can be selected to obtain only those polyclonal antibodies that are specifically immunoreactive with marker "X" and not with other proteins, except for polymorphic variants and alleles of marker "X". This selection may be achieved by subtracting out antibodies that cross-react with marker "X" molecules from other species. A variety of immunoassay formats may be used to select antibodies specifically immunoreactive with a particular protein. For example, solid-phase ELISA immunoassays are routinely used to select antibodies specifically immunoreactive with a protein (see, e.g., Harlow & Lane, Antibodies, A Laboratory Manual (1988), for a description of immunoassay formats and conditions that can be used to determine specific immunoreactivity). ***Typically*** a specific or selective reaction

> will be at least twice background signal or noise and more typically more than 10 to 100 times background." (See instant specification at page 18, 2nd paragraph, emphasis added).

Given this extremely relative, and therefore broad, description of "specific binding" in the instant specification, the phrase "an isolated antibody which ***specifically binds*** to the amino acid sequence comprising RSATEEEPPNDD of the α-subunit of (Na^++K^+)-ATPase…" given its broadest reasonable interpretation consistent with the instant specification has been considered as no more limiting than the previous incarnation of claim 1 which read: "an isolated antibody which ***recognizes*** the amino acid sequence comprising RSATEEEPPNDD of the α-subunit of (Na^++K^+)-ATPase…" .

In conclusion, the instant claims are rejected as anticipated by Arystarkhova, as evidenced by Bost, Bendayan and the instant specification.

Since the Office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibodies fail to specifically bind to the amino acid sequence comprising RSATEEEPPNDD of the α-subunit of (Na^++K^+)-ATPase wherein binding of the antibody to the amino acid sequence RSATEEEPPNDD of the α-subunit of (Na^++K^+)-ATPase increases myocyte intracellular diastolic and systolic calcium. See *In re Best*, 195 USPQ 430, 433 (CCPA 1977); *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983); *In re Fitzgerald* et al., 205 USPQ 594 (CCPA 1980).

Moreover, it is noted that claim 7 recites, "the antibody of claim 1, wherein the antibody is administered to a patient...suffering from or susceptible to heart disease and/or muscle contractile disorders," which, given its broadest reasonable interpretation consistent with the instant specification, reads on administration to most of the industrialized world since most of the industrialized world is susceptible to heart disease as it is the most frequent cause of death in the industrialized world. Moreover, the "wherein..." recitation in claim 7 is an intended use of the claimed antibody, and if the prior art structure is capable of performing the intended use, then it meets the claim. In re Casey , 152 USPQ 235 (CCPA 1967); In re Otto, 136 USPQ 458, 459 (CCPA 1963).

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZACHARY SKELDING whose telephone number is (571)272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.

   If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Zachary Skelding, Ph.D.
Patent Examiner
June 4, 2008

/Michail A Belyavskyi/
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